A CASE OF RAPIDLY FATAL CEREBRITIS, RESEMBLING CEREBRO-SPINAL MENINGITIS, WITH EXHIBITION OF SECTIONS OF THE CEREBRUM, MID-BRAIN, PONS, AND POST-OBLONGATA.

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CLINICAL REPORT BY DR. LLOYD.

IT has long been a well recognized fact that cases of sporadic spotted fever occur. This purely clinical observation is based largely upon the fact that isolated cases of obscure infection arise now and then, and present certain superficial resemblances, which have led to their being included in one group and dubbed cerebro-spinal meningitis. The exact nature of the infection in these cases is still practically unknown; and, in fact, it may even be a question whether all these reported cases are due to an identical microbe. Rapid fulminating infecting is an occasional characteristic, we know, of many specific micro-organisms. Thus we may instance the germs of measles, scarlatina, typhoid fever, small-pox and even pneumonia. In the cases of all these diseases we occasionally see instances of extreme virulence, in which many symptoms in common are presented and in which the result is invariably fatal. The most common symptoms are high fever, delirium, poisoning of the cardiac and respiratory centres, asthenia, and, in the cases of the exanthems, a hæmorrhagic or purpuric eruption. Deducting these more or less familiar diseases, there remain several varieties of obscure infection, largely attacking the cerebro-spinal system, which present also some of these common symptoms, but which cannot as yet be classed satisfactorily in any nosological group. One of these is the alarming disease known as acute delirium. I once saw a vigorous young man die of this affection after an illness of but sixty-two hours. The autopsy revealed no gross lesion of any organ of his body. The acute delirious mania of alienists—such cases, for instance, as occur sometimes in the puerperium or after gynæcological operations—are doubtless due to some form of infection whose life history is not yet well understood. Again, virulent cases of purpura hæmorrhagica occur, and present many symptoms suggestive of systemic infection. Thus the constitutional reaction, the extreme cephalalgia and rachialgia, the depraved state of the blood shown by the copious hæmorrhages from mucous and serous surfaces, and the purpuric eruption in the skin, all point to the action of some poison. The resemblances, in fact, between grave purpura hæmorrhagica and some cases of spotted fever seem to me to be far from superficial, and were impressed upon my mind especially in the case which is about to be reported. Finally, we may instance the overwhelming doses of the malarial plasmodium, which fortunately are but rarely seen in this latitude.

From these considerations it seems that one of the many great desiderata in pathology at present is to obtain more light, first, upon the distinct action of all infecting agents upon the tissues, especially of the cerebrospinal system; and, second, to detect, describe and differentiate such of these microbes as are still unknown. In other words it has become essential for us to no longer confine ourselves so exclusively as heretofore to the mere clinical field, with all its classical descriptions and distinctions; but to undertake in every possible case to study the distinct action on the nervous and other tissue of these infecting agents, some of which apparently have not yet received even a satisfactory name. It is possible that the description of meningitis, cerebritis and even myelitis will yet have to be, in part at least, rewritten, in order to have it conform to the constantly widening field of microbian pathology.

These observations apply especially. it seems to me, to that group of cases included under the heading of sporadic cerebro-spinal meningitis. Cases described under this heading vary considerably, and the diagnosis of some of them is left very obscure by the clinical descriptions of some writers. Without more detailed pathological studies, cases of this general type, I maintain, must often remain in doubt. The mere presence of a petechial eruption, combined with high fever and delirium, is not enough to convince us that we have a simple clinical, much less a simple pathological, question to solve. These cases vary widely in type. In some the element of meningitis is almost absent; in fact, there appears to be a type of cases in which a disseminated focal process is present in the cerebral and medullary tissue proper. In these cases the evidence of focal lesions is often present, as in one or more of the cranial nerves. Another rare form of the disease presents almost exclusively a lesion of the spinal cord, causing paraplegia. Moreover, in some cases, other organs in the body, as the lungs, heart and kidneys, may show indubitably the evidence of the action of some infecting agent. In some cases the inflammatory process is distinctly hemorrhagic, as described by Strümpell.

As for the particular microbe in these cases, it is well known that the diplococcus, so often found associated with pneumonia, has been found in the lymph spaces and in collections under the pia in sporadic cases of cerebro-spinal meningitis. That it is invariably present, much less that it is the invariable cause of these various forms of virulent hæmorrhagic and disseminated focal cerebritis, is doubtful. This is not the place to enter into a lengthy critique of the literature of this subject; it may suffice to say that for the present the bacteriology of the subject must be left for determination to those skilled in this work, while we still for sometime devote ourselves to the study of the morbid anatomy.

The history of the case, upon which this study is based, is as follows:

C. T., aged about 26; white, male; an architect by occupation, was seized abruptly on January 9th with a severe chill. High fever supervened and the man, feeling extremely ill, took to his bed at once. He had severe headache and pains in the back and limbs. There was no history of vomiting or convulsion. Within twenty-four hours he grew delirious, and, from reports, already presented the appearance of grave illness. As far as could be gathered from his family and friends, the patient had not been exposed to any source of infection or to any unusual conditions to their knowledge.

He was treated at his home in this city during the first three days, and the report of the earlier progress of his disease is meagre and unsatisfactory. It was apparently thought that the patient was developing typhoid fever, and he was treated accordingly. The only note of interest was that on the third day it was observed that the patient's left upper eye-lid drooped and that the left eye was turned outwards. A spot of ecchymosis appeared also at this time below the left eye.

On January 13th, the fourth day of his disease, the man was admitted into the Methodist Hospital under the writer's care. He was then gravely ill. He was in a pronounced "typhoid" state, with great depression, and was streporous and delirious. He had a dry tongue, a rapid pulse and a continued fever. The most conspicuous symptom was a complete paralysis of the left third nerve. The lid drooped, the ball was turned outwards and the pupil was dilated. This at once attracted my notice, and I called attention to its being practically an unknown symptom in typhoid fever, the disease for which the patient had been admitted to the hospital. There was at the same time some tonic spasm of the muscles of the jaw, giving an expression of trismus, especially when the patient attempted to speak. There was also a rose colored eruption over the malar bone. With the exception of this trismus and a hyperæsthetic state of the surface of the trunk there were not noticed at this time or later any symptoms of marked irritation of either the nerve centres or the meninges. There was never any retraction of the head or fixation of muscles such as is so frequently described as being present in epidemics of spotted fever.

The diagnosis of the disease remained obscure during the first afternoon and night that the patient passed in the hospital. Typhoid fever, unless of a very aberrant and fulminant type, did not seem indicated. The disease had begun too abruptly, and the absence of abdominal symptoms, and the presence of the paralysis of the third nerve contra indicated enteric fever. The appearance of an eruption during the night cleared up this question of diagnosis to some extent. This eruption began as small papules on the face and forehead. These rapidly developed and increased in number so that by night time the whole body was covered with them. A large spot on the malar bone increased in size and soon became petechial, and by night all the papules became darker and showed hemorrhage into the tissues. During the first day in hospital hiccough was an occasional symptom.

The extensive petechial eruption, consisting of small puplish spots, was scattered thickly over face, limbs and trunk. These spots were little, if at all elevated above the surface of the skin. They evidently consisted of small hemorrhagic effusions. They varied in size from that of a millet seed to that of a duck shot.

Over the left eye, and on the forehead and about the lips were large ecchymoses—as large in some instances as a silver half-dollar. On the dorsum of either hand was a large swelling much resembling erythema nodosum. A single pustule was seen over the left ear. The pulse was now rapid and compressible, and the nervous condition one of semi coma. The patient grew steadily worse, and on the second day after admission (fifth day of disease) he vomited a brown, bloody fluid. At this time also blood, pus and casts were found in his urine. About fifteen minutes before his death he vomited almost a pint of this bloody fluid. His death occurred in deep coma on the third day in hospital and sixth day of his disease. There was never any cardiac, pulmonary, or intestinal involvement.

In arriving at diagnosis in this case, I had to consider the abrupt onset with a chill, the rapidly grave course, the paralysis of a cranial nerve (the third), the semi-coma and depression, and finally the eruption. The absence of so-called "meningeal" symptoms, as retraction of the head, was marked; but in line with such irritative symptoms was the trismus. Measles was excluded by the absence of all catarrhal symptoms in the respiratory passages, and by the absence of the crescentric and swollen rash so characteristic of that disease. Malignant small pox was not considered at all possible, because, although the eruption appeared about the fourth day, most careful observation failed to detect a characteristic umbilicated pustule anywhere on the patient's body. It hardly seemed possible that, if the case was one of small-pox, there should not be even one distinct pock. The eruption, moreover, was not elevated or shot like. Against both of these diseases was complete unilateral third nerve palsy, which appeared as early as the third day.

The acute nephritis was clearly indicative of a profound blood poisoning. It seemed clear that the clinical picture, while not quite typical, could be fairly included only in the group of cases called sporadic spotted fever; and so it was diagnosticated, treated and reported.

Autopsy.—Petechia were seen on the face and hands, and scattered less thickly over the body. The heart was normal, no ulcerative endocarditis. The lungs were normal. No lesions demonstrated in the liver. Extravasations of blood into mucous membranes of the stomach and intestines were seen. Both kidneys were much enlarged and were purplish in color, and the tubules were packed with pus, presenting the appearance of acute purulent nephritis. The capsule of the kidneys was not adherent.

Brain.—There was some extravasation of leucocytes into the perivascular sheaths of dura and pia. The meninges were slightly opaque. In the left occipital lobe in the region of the cuneus, there was found a liquified blood clot, not apparently purulent. This cavity was of recent origin—and of the size of a small marble.

Another small area of softened blood clot of recent inflammatory origin was found in the anterior lobe just in front of the ascending frontal convolution.

Some regions presented the appearance of deep congestion of the soft membrane.

In the mid-brain, on the left side, about the region of the third nerve nuclei, there was the appearance of large punctate hæmorrhages.

A second spot of necrosis and softening was found in the left occipital lobe. Pus was squeezed out of this.

There was a hæmorrhage under the scalp on the left side. Hæmorrhagic spots in the spinal dura were also found.

MICROSCOPICAL REPORT BY DR. SAILER.

The specimens of the present case, saved from examination, consisted of the crura, the pons, the medulla, and the spinal cord. It was impossible, unfortunately, to place them in alcohol until about twenty four hours after removal, and by that time all the tissues seemed to be quite dry. The case was supposed to be one of sporadic cerebro spinal meningitis, but aside from rather pronounced injection, the membrane appeared to be normal. Small hope was entertained of getting any satisfactory results, but, contrary to expectations (after passing the tissues rapidly through the alcohols and then allowing them to remain some weeks in celloidin) the sections stained very well; both with methylen blue (Nissl's method) and hæmatoxylin.

The following changes were found:

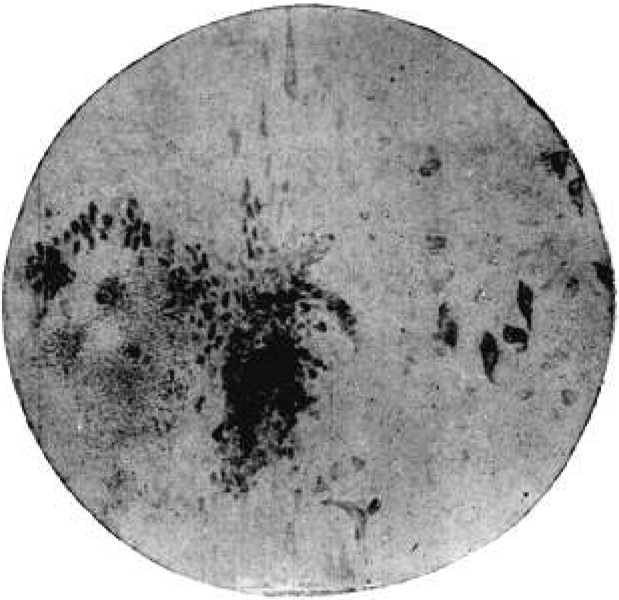
The pia mater of the cord is slightly thickened; the vessels, particularly those of the cervical region, are dilated and filled with blood, which appears to contain a considerable proportion of leucocytes; and in the neighborhood of some of the vessels there is a very slight accumulation of round cells. The tissue of the pia itself is only slightly infiltrated with leucocytes and not at any place adherent to the substance of the cord; the greatest amount of infiltration is found in the anterior septum. The ependymal cells of the central canal have undergone considerable proliferation, being arranged throughout the entire cord in a sort of rough T shape; the short stem being directed posteriorly; in the lumbar region the central canal is distinctly doubled. The larger intrinsic vessels of the cord appear to be unaffected. There is no increase in their number and those that are present are not dilated nor surrounded by collections of round cells. One of the vessels of the column of Burdach that was cut longitudinally, shows a slight accumulation of round cells in the perivascular lymph space.

The distinctive pathological alteration is a round cell infiltration of the gray and white matter of the cord. Here and there throughout the cord are minute foci of round cells, usually round in outline, and not sharply limited, but gradually diminishing into the surrounding tissue. These foci are composed of simple polynuclear cells with deeply staining nucleii, none of them containing any oxyphilic granula. Some detritus is also found and occasionally, a body that appears to be a partially disintegrated nerve cell A considerable number of polynuclear cells are also found scattered singly through the tissues. Of these foci two or three may usually be found in any section, more restricted, in the lower part of the cord, to the gray matter, but, above the lumbar region, affecting the gray or white matter indifferently. A single large focus, occupying about half the gray commissure, is found in the lumbar cord. The centre of the focus frequently contains the remains of an obliterated capillary and some of the still patulous capillaries of the cord are surrounded by a few round cells. The ganglion cells occasionally show evidences of slight degeneration; the cell body stains diffusely, the outline is more irregular and the processes apparently lost. As a rule, however, the chromophilic bodies are clearly stained and of normal shape and arrangement; and the nucleus, stained with hæmatoxylin, shows no abnormality. It may be remarked, that, owing to the condition in which the specimen was received and the doubt that it would prove of any interest, no pieces were prepared for the Golgi method, and it is therefore impossible to speak of finer ramifications of the protoplasmic processes, where, according to Monti, cellular degeneration resulting from vascular change is always first manifest. The changes in the medulla are essentially similar to those of the cord. The ependyma of the floor of the fourth ventricle is thickened, and the foci of round cells are distributed generally throughout the various tissues. The ganglion cells of the hypoglossal nucleus exhibit slight changes that are possibly degenerative. The chromophilic bodies are more irregular in outline, and occasionally there is a little mass of deeply staining material heaped to one side of the nucleus, while the chromophilic bodies elsewhere are more scattered. This form of degeneration has been described by Sarbo as occurring in the cells of the anterior cornua after compression of the abdominal aorta. The nuclei of these cells, when stained with hæmatoxylin, contain chromatin that is slightly coarser and less distinct than is normal. Such cells as happen to be in the midst of a focus show greater degenerative changes; the outlines becoming indistinct, the cells pale, and the chromophilic bodies disappearing. The tissue about the aqueductus Sylvii was soft and crumbled under the section knife, so that no examination could be made of the oculo motor nucleus. In the left crura a very large focus was found, occupying the inner half of the substantia nigra and the white matter on either side. The tissue in the neighborhood of this lesion had undergone considerable alteration, and the large pyramidal cells of the substantia nigra had reached an extreme degree of degeneration. The chromophilic bodies no longer appear; the nucleus is stained a faint homogeneous blue, and the nucleolus is absent. The processes are irregular and varicose. A peculiar appearance is caused by combination of the yellow pigment normal to these cells with the blue of the stain, so that the cell seems to be filled with fine, green granulations. The rest of the left crus contains a number of other lesions of similar but less extensive nature, whilst the right crus is but slightly involved. No hemorrhages were found in the tissue of the brain or cord. The examination of the micro-organisms was negative. It could not be determined that the neuroglia cells were increased. The case may be considered as one of disease of the connective or mesoblastic tissues of the central nervous system, produced by some infectious agent introduced through the vascular system. The nervous tissues proper, that is, the tissues derived from the epiblast, were only secondarily affected.

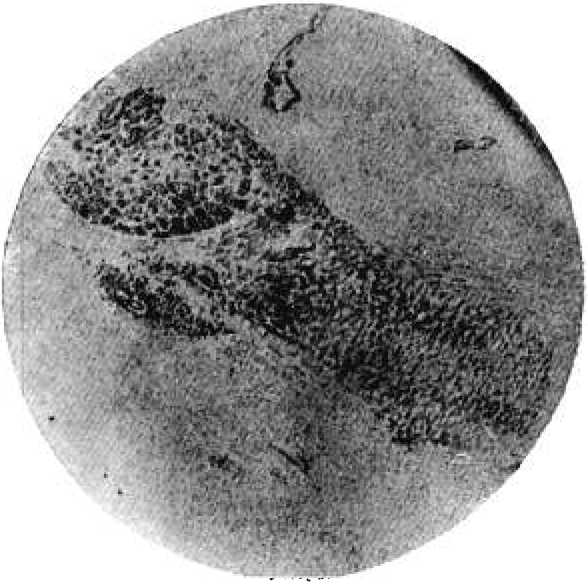
In 1890 there appeared in the *Deutsch. Archiv für* *klinische Medicin*. Strümpell's paper, now classical, "On Acute Primary Encephalitis." The changes found constituted a pathological condition that until then had not been recognized. They consisted of a round cell infiltration proceeding from the vessels and affecting particularly the white matter of the brain. The ganglion cells were normal and the neuroglia cells did not appear to be swollen. Friedman, however, had previously classified the forms of acute encephalitis into a suppurative form due to infectious irritants, an inflammation of the tissues after the use of caustics leading to proliferation of the large cells, and a creeping interstitial encephalitis combined with necrobiosis after aseptic injury, and he believed that in acute non-suppurative inflamation, the inflamatory new formation corresponds chiefly to proliferation of the fixed tissues. It is unquestionable that Friedmann's first group includes a condition which would closely resemble the acute encephalitis of Strümpell. It is, of course, possible for an infectious principal to attack the vascular systems of the brain, instead of the meninges, or that both should be equally affected, and it had already been noted by Strümpell and Osler that in epidemics of cerebro-spinal meningitis, cases occurred in which no lesion was found in the membranes at the autopsy, whose clinical histories, however, were similar to those in which the characteristic lesions had been discovered. Osler attempted to explain this by supposing that the stage of exudation had not had time to devolop.

Birch-Hirschfeld describes a form of encephalitis in which there are no microscopic changes, but which are characterized microscopically by the infiltration of round cells in the adventitia of the larger vessels, and in the immediate neighborhood of the minute capillaries, frequently with hemorrhages into these infiltrated areas. Cases corresponding to this description have been reported; one by von Jaksch, that deserves mention, because, despite careful search no micro-organisms could be found in the affected tissues.

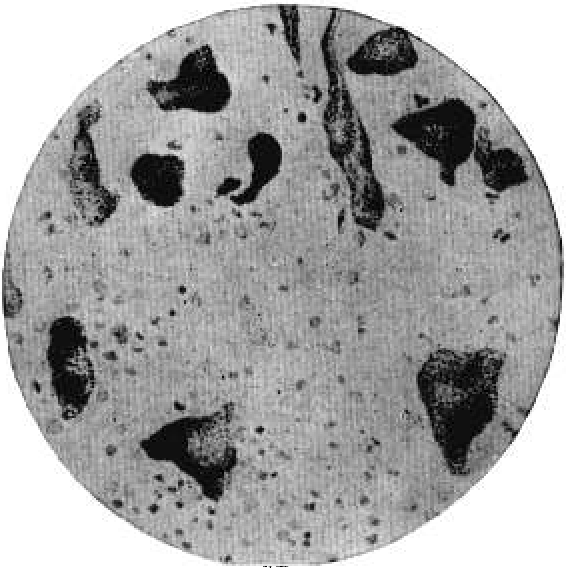
Drexler has reported the case of a small dog with great care. The disease lasted at least seven weeks and was characterized by local spasms and paralysis. Besides a few slight evidences of meningitis, the chief lesions were two large collections of round cells and detritus, one in the pons and one in the medulla; numerous circumscribed collections of round cells and considerable interstitial infiltration. The ganglion cells in the neigh-



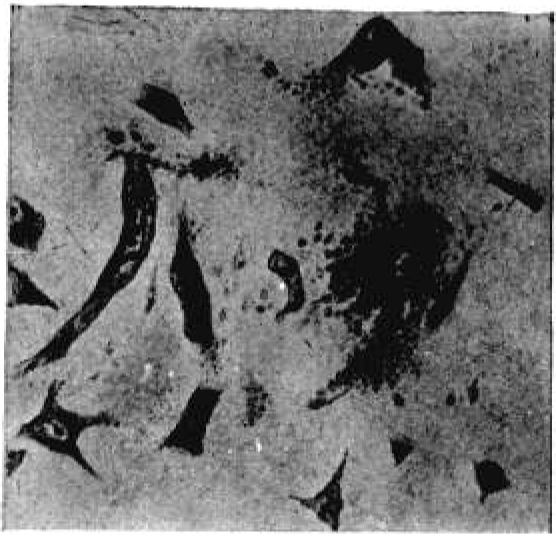
Mass of round cells in posterior columns of spinal cord (dorsal region).



Mass of round cells in gray commissure of spinal cord (lumbar region).



Degenerated cells from neighborhood of abscess in left crus.



Group of round cells in hypoglossal nucleus.

borhood of the focal lesions showed signs of partial or complete destruction. The connective tissues are of late taking a more important part in the pathology of the central nervous system, and their alterations play a principal role in the, as yet, supposititious morbid anatomy of paralysis agitans, chronic chorea and idiocy. The present case must be included among the acute conditions and can probably be best described as acute interstitial encephalitis.

DISCUSSION.

Dr. OSLER.—I am sorry that we have not a more detailed reference to the condition of the kidney. From the report, it may have been a case of cryptogenetic septicæmia. With reference to the diagnosis of meningitis or encephalitis in these cases, it is well to bear in mind that there is no single symptom, indeed, no group of symptoms, which can be depended on to show involvement of the cortex cerebri. There may be retraction of the head, a spastic condition of the muscles, clonic or tonic spasms, delirium, and unless the basilar meninges are involved the diagnosis is most uncertain. I reported a case last year in which there was scarcely a symptom lacking of cerebrospinal meningitis, even clonic and tonic spasms of one arm, with great retraction of the head. The autopsy showed the lesions of typhoid fever without a trace of macroscopical change in the brain or cord. The question is, of course, whether in such cases, in which there are no coarse changes, there may not be found by newer methods, most extensive lesions, the direct effect of the toxines.

Dr. J. J. PUTNAM; said: I have been very much impressed with what Dr. Osler has said. The fact that we may get the symptoms usually attributed to meningitis without meningitis, is certainly an addition to our clinical knowledge. In diphtheritic paralysis some of the most recent observers have failed to find any lesions, although the characteristic symptoms have been present.

Dr. THEODORE DILLER, said: I have been struck with what seems to me to be probably an important truth, concerning cerebrites, as reported by Drs. Putnam and Lloyd, typhomania on the one hand and Landry's paralysis on the other hand. Certain bacteria or ptomaines may produce certain lesions and certain clinical symptoms. They may attack the convexity at one time and the base at another. Then, too, it is probable that the same bacterium or ptomaine may produce in different individuals widely different pathological changes and symptoms. I think this theory gives us a sort of working hypothesis, by which we can account for the great variations seen in Landry's paralysis and in these cases of cerebritis, meningo-cerebritis and typhomania or delirium grave. There is here a rich field for bacteriologic and chemical examinations, and we may expect them to clear up much that is now very obscure.

Dr. LLOYD in closing the discussion said: I am glad that Dr. Osler emphasized the point that he did. I have felt that an accurate diagnosis of the identity of the infecting agent in many of these cases was doubtful, and have reported this case as one of cerebritis, presenting only the symptoms of cerebro-spinal meningitis. I have abstained from giving a name to the active agent. I thought, perhaps, the pus that was present was the result of an epi-infection and that the pus-making micrococcus had acted secondarily. In the infectious diseases it is a very grave question often in these explosive cases to establish the diagnosis. My object in bringing this case forward was simply to present a pathological study.